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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/802,682	03/17/2004	Akira Asakura	13735 US1 (C038435/010970)	9826
7590	12/01/2004		EXAMINER	
Stephen M. Haracz, Esq. BRYAN CAVE LLP 1290 Avenue of the Americas New York, NY 10104-3300			WALICKA, MALGORZATA A	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 12/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/802,682

Applicant(s)

ASAKURA ET AL.

Examiner

Malgorzata A. Walicka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,9,22,25 and 28-31 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-3,9,22,25 and 28-31 is/are rejected.
- 7) ☒ Claim(s) 29 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 06/25/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: allowable subject matter.

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The examiner acknowledges the Application and preliminary amendment filed March 17, 2004. Claims 4-8, 10-19, 23-24 and 26-27 are canceled; new claims 29-31 are added. Claims 1-3, 9, 20-22, 25, 28-31 are pending and are the subject of this office Action.

DETAILED ACTION

1. Restriction/election

This application contains claims directed to the following patentably distinct species of the claimed invention: polypeptides set forth by SEQ ID NO: 5, 6, 7 and 8 having alcohol and aldehyde dehydrogenase.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-3, 9, 20-22, 25, 28-31 are generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

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Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Applicants representative Gonzalo Merino on November 16 2004 a provisional election was made without traverse to prosecute the invention of polypeptide of SEQ ID NO: 8, Claim 1-3, 9, 20-22, 25, 28-31. Affirmation of this election must be made by applicant in replying to this Office action.

1. Priority

Acknowledgment is made of Applicant's claim for priority based on European Patent Office (EPO) 96115001.8 filed September 19, 1996. However priority document is absent from the record.

It is noted that this application appears to claim subject matter disclosed in prior Application No. 09/470667, filed 12/22/1999 now patented, and to Application No. 08/934,506 now abandoned. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-

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in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The

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Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.
on page 3 of the Supplemental Sheet. See 37 CFR 1.52(c).

2. Objections

2.1. Specification

Sequence Rules

The instant specification on page 31, lines 13 and 15, and on page 40, line 24 and 26, present amino acid and nucleotide sequences that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), but fails to comply with the requirements. According to 37 CFR 1.821-825, every disclosed amino acid sequence of four or more residues or 10 or more nucleotides must be identified by a SEQ ID NO. The amino acid sequences presented do not have SEQ ID NOs. In order to comply with the sequence rules Applicants must identify these sequences by providing sequence identification numbers, and provide a new version of the sequence listing and disk.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

3. Rejections

3.1. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-3, 20-22, 25, 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear whether the enzyme has the same function as that of the recombinant polypeptides comprised by the enzyme. The examiner suggests adding the description of the activity of the enzyme in the claims immediately after the word "enzyme". For examination purposes it is assumed that any enzyme claimed and/or used has alcohol and aldehyde dehydrogenase activity.

3.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.1.1. Lack of written description

Claims 2-3 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 2 and 3 are directed to an enzyme that comprises a combination of, at least two amino acids sequences each of said sequences being selected from the group consisting of SEQ ID NO: 8, SEQ ID NOs: 5, 6, 7 and amino acid sequences that are at least 80% identical to SEQ ID NO: 8, SEQ ID NOs: 5, 6 and 7. In the simplest version the claimed genera of enzymes comprise, due to election of SEQ ID NO: 8,

- a) SEQ ID NO:8 and SEQ ID NO: 5,
- b) SEQ ID NO: 8 and SEQ ID NO: 6,
- c) SEQ ID NO: 8 and SEQ ID NO: 7,
- d) SEQ ID NO: 8 and SEQ ID NO: 8,

e) SEQ ID NO: 8 and an amino acid sequence that is at least 80% identical to SEQ IDNO: 5,

f) SEQ ID NO: 8 and amino acid sequence that is at least 80% identical to SEQ ID NO: 6,

g) SEQ ID NO: 8 and amino acid sequence that is at least 80% identical to SEQ ID NO: 6

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g) SEQ ID NO: 8 and amino acid sequence that is at least 80% identical to SEQ ID NO: 6

h) SEQ ID NO: 8 and amino acid sequence that is at least 80% identical to SEQ ID NO: 7,

i) SEQ ID NO: 8 and amino acid sequence that is at least 80% identical to SEQ ID NO: 8,

j) an amino acid sequence that is at least 80% identical to sequence NO: 8 and SEQ ID NO: 5,

k) an amino acid sequence that is at least 80% identical to sequence NO: 8 and SEQ ID NO: 6

l) an amino acid sequence that is at least 80% identical to sequence NO: 8 and SEQ ID NO: 7, and

m) an amino acid sequence that is at least 80% identical to sequence NO: 8 and SEQ ID NO: 8.

The specification discloses, on Fig. 3, expression vectors pSSAB201 and pSSBA201 that encode a chimera comprising genes encoding SEQ ID NO: 8 and SEQ ID NO: 5. However, neither the amino acid and nucleotide structure nor the function of the chimeras encoded by pSSAB201 and pSSBA201 are disclosed. Provision of pSSAB201 and pSSBA201 is not sufficient to identify even a single representative species of the claimed genus. Thus, because applicants did not disclose identifying characteristics of claimed genera of chimeric enzymes and thus the methods of their

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use, one skilled in the art is not convinced that the Inventors were in possession of claimed invention at the time of filing of the instant application.

Claim 9 is rejected under 35 U.S.C. § 112, first paragraph, because the specification is lacking the description of biologic deposit. The invention appears to employ a novel gene and plasmid, pSSB103R. Since the plasmid is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The sequence of claimed plasmid is not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirement of 35 U.S.C. § 112 may be satisfied by deposit of the plasmid or transformed cell. The specification does not disclose a repeatable process to obtain the plasmid and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of the plasmid should have been made in accordance with 37 C.F.R. § 1.801-1.809.

If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by the applicant, or a statement by an attorney of record over his/her signature and registration number, stating that the specific microorganism has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to

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certify that the deposit meets the criteria set forth in 37 C.F.R. § 1.801-1.809, the applicant may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his/her signature and registration number, showing that:

- (1) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
- (2) all restriction upon availability to the public will be irrevocably removed upon granting of the patent;
- (3) the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and
- (4) the deposit will be replaced if it should ever become inviable.

2.2.2. Scope of enablement

Claims 1-3, 9, 20-22, 25, 28, 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the alcohol and aldehyde dehydrogenase of SEQ ID NO: 5, 6, 7, and 8 that are in at least 80% identical to each other, does not reasonably provide enablement for any amino acid sequence comprising a sequence that has at least 80% identity to SEQ ID NO: 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to a large number of polypeptides claimed. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompass any enzyme, form any natural or man-made source, having alcohol and aldehyde dehydrogenase activity, as well as to a genus of the methods of their use, wherein the enzyme comprises a sequence that is at least 80% identical to SEQ ID NO: 8. While methods of gene cloning, gene structure manipulations, expression and determination of enzymatic activity of alcohol and aldehyde dehydrogenase are well known in the relevant art, and skills of the artisans highly developed, no one is able to make the claimed invention. The lack of the structural characteristics of said polypeptides and encoding polynucleotides makes the probability of success in obtaining the claimed invention low. The specification teaches SEQ ID NO: 5, 6, 7, and 8 that are alcohol and aldehyde dehydrogenases obtained from *Gluconobacter oxydans*. All these enzymes are in at least 80% identical to each other. Providing these 4 representative species of the

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genus does not provide the identifying characteristics of all the enzymes encompass in the scope of the claims. Applicants do not teach, with exception of instruction for conservative substitutions, how to obtain, from SEQ ID NO: 8 a sequences that is only 80% identical to sequence of SEQ ID NO: 8 and still retains its property.

Examiner concludes that without the further guidance on the part of Applicants in regards to the structure of the claimed polypeptides and method of their use, experimentation left to those in the art is improperly extensive and undue.

In addition, claim 2 and 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the plasmid comprising genes encoding SEQ ID NO: 5 and SEQ ID NO: 8 (plasmids pSSAB201 and pSSBA201), does not reasonably provide enablement for an enzyme that comprises a combination of at least two amino acids sequences each of said sequences being selected from the group of SEQ ID NO: 8, SEQ ID NOs: 5, 6, 7, and amino acid sequences that are at least 80% identical to SEQ ID NO:8, SEQ ID NOs: 5-7 or a sequence that is at least 80% identical to SEQ ID NO:8. In the simplest version the claimed genera of enzymes comprise, due to election of SEQ ID NO: 8,

- a) SEQ ID NO: 8 and SEQ ID NO: 5,
- b) SEQ ID NO: 8 and SEQ ID NO: 6,
- c) SEQ ID NO: 8 and SEQ ID NO: 7,
- d) SEQ ID NO: 8 and SEQ ID NO: 8,

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e) SEQ ID NO: 8 and an amino acid sequence that is at least 80% identical to SEQ IDNO: 5,

f) SEQ ID NO: 8 and amino acid sequence that is at least 80% identical to SEQ ID NO: 6,

g) SEQ ID NO: 8 and amino acid sequence that is at least 80% identical to SEQ ID NO: 6

h) SEQ ID NO: 8 and amino acid sequence that is at least 80% identical to SEQ ID NO: 7,

i) SEQ ID NO: 8 and amino acid sequence that is at least 80% identical to SEQ ID NO: 8,

j) an amino acid sequence that is at least 80% identical to sequence NO: 8 and SEQ ID NO: 5,

k) an amino acid sequence that is at least 80% identical to sequence NO: 8 and SEQ ID NO: 6

l) an amino acid sequence that is at least 80% identical to sequence NO: 8 and SEQ ID NO: 7, and

m) An amino acid sequence that is at least 80% identical to sequence NO:8 and SEQ ID NO: 8.

The claims are also directed to the use of the above enzymes.

The claims are broader than the enablement provided by the disclosure with regard to large number combinations of polypeptides claimed. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166

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USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompass an enzyme comprising any combination of at least two enzymes, from any natural or man-made source, having alcohol and aldehyde dehydrogenase activity, as well as to a genus of the methods of their use, wherein the enzyme comprises a combination of at least two polypeptides as listed under a) to m). While methods of gene cloning, gene structure manipulations, expression and determination of enzymatic activity of alcohol and aldehyde dehydrogenase are well known in the relevant art, and skills of the artisans highly developed, no one is able to make the claimed invention. The lack of the structural characteristics of said polypeptides and their combinations makes the probability of success in obtaining the claimed invention low. The specification discloses, on Fig. 3, expression vectors pSSAB201 and pSSBA201 that encode a chimera comprising genes encoding SEQ ID NO: 8 and SEQ ID NO: 5. However, neither the amino acid nor nucleotide structure of the chimeras encoded by pSSAB201 and pSSBA201 are disclosed by Applicants. Thus, because the nucleotide sequences

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of pSSAB201 and pSSBA201 are not disclosed on skilled in the art is not instructed how to make even one claimed chimera. Without a further guidance on the part of Applicants related to the structure of chimeric enzymes, one skilled in the art is forced to construct numerous combinations of disclosed sequences, expressed them and check the enzymatic activity of the expressed construct with a low probability of success.

Without a further guidance on the part of Applicants in regards to the structure of the claimed chimeras, experimentation left to those in the art is improperly extensive and undue.

3. Conclusion

No claim is in condition for allowance. Claim 29 is objected to as being dependent upon the rejected base claim 1, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

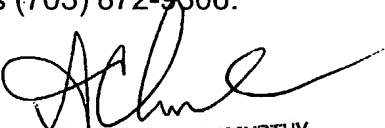
The following is a statement of reasons for the indication of allowable subject matter: Applicants disclose a novel enzyme from *Gluconobacter oxydans*; the enzyme is encoded by polynucleotide sequence of SEQ ID NO: 4 and is set forth by the amino acid sequence of SEQ ID NO: 8. The enzyme is useful in recombinant production of many chemical compounds such as aldehydes, carboxylic acids and ketones, especially, 2-keto-L-gluconic acid. No prior art teaches of fairly suggests the invention.

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As allowable subject matter has been indicated, applicant's reply must either comply with all formal requirements or specifically traverse each requirement not complied with. See 37 CFR 1.111(b) and MPEP § 707.07(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-1600. The fax phone number for this Group is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 872-9306.

Malgorzata A. Walicka, Ph.D.
Patent Examiner
Art Unit 1652


PONNATHAPURA ACHUTAMURTHY
SUPERVISOR
TECHNICAL STAFF 1600

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Application No.: 10/802,682**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING
NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a Sequence Listing as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the Sequence Listing in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the Sequence Listing in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up Raw Sequence Listing.
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the Sequence Listing is not the same as the computer readable form of the Sequence Listing as required by 37 C.F.R. 1.821(e).
- ☒ 7. Other: the amino acid and/or nucleotide sequences on page 31, lines 13 and 15, and on page 40, line 24 and 26 are lacking from the sequence listing.

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the ☐ Sequence Listing ☐.
- ☒ An initial or substitute paper copy of the Sequence Listing, as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

For Patent software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE